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Immunoglobulins and Sepsis

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Author contributions

All authors developed the outline. MSH wrote the first draft. All authors contributed to the critical revision of the manuscript for important intellectual content.

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Intravenous immunoglobulins are considered as potential adjuvant therapy in sepsis patients. We present a narrative review of recent research into the associations between immunoglobulins and sepsis.

Immunoglobulins and free light chains

Immunoglobulins are glycoproteins secreted by plasma cells. Each immunoglobulin molecule monomer consists of identical heavy and light chain pairs held together by electrostatic forces and disulphide bonds. Based on their heavy chain, there are five immunoglobulin isotypes namely IgG, IgA, IgM, IgD and IgE [1]. There are two types of light chains (kappa and lambda), which are also present in circulation independent of whole immunoglobulin molecules, referred to as free light chains (FLC). The *Variable* regions of immunoglobulin molecules enable cross-linking to bacterial and other antigens (antigen binding). The *Constant* region transduces signals in response to antigen binding (effector function). IgG has four subclasses (IgG1, IgG2, IgG3, and IgG4) and the main functions are secondary antibody responses, opsonisation and complement activation. IgA has two subclasses (IgA1, IgA2) and the main function is mucosal immunity. The key functions of IgM are complement activation and primary antibody responses.

Low immunoglobulins and high free light chains are common in sepsis

Low immunoglobulin concentrations [2] as well as abnormally high FLC levels [3] are seen in most adult sepsis patients. Although, low IgG is the commonest quantitative immunoglobulin abnormality in sepsis, a number of reasons explain why low IgG alone does not increase the risk of death in sepsis patients [2]. First, the nadir of immunoglobulin drop is often seen on day 3 following sepsis diagnosis [2, 3]. Second, low levels of multiple endogenous immunoglobulins (IgG1, IgM and IgA) may be required to increase the risk of death [2-4]. Third, the association between low immunoglobulins and mortality is observed in sepsis patients with less severe organ dysfunction [5]. These reasons suggest that the risk of death *caused* by low immunoglobulins is either lower than other stronger risk factors such as organ dysfunction / comorbidity in sepsis patients or that our understanding of the mechanisms behind this high prevalence of low immunoglobulins in sepsis is incomplete. For example, endothelial abnormalities in sepsis include endothelial dysfunction and endothelial apoptosis leading to leaky capillaries. IgG and albumin are recycled through the Fc neonatal receptors in endothelial cells. There may also be impaired immunoglobulin recycling and leak of immunoglobulin into the extra vascular space resulting in low immunoglobulin levels [1].

Immunoglobulin consumption secondary to pathogen opsonisation and neutralisation of toxins could also contribute to low immunoglobulin levels. There is impaired in vitro IgM production by lymphocytes from sepsis patients [6]. In health, light chains are produced in excess of heavy chains. Raised light chains are surrogates for new immunoglobulin production [7]. Therefore, the observation that low immunoglobulin levels with concurrent raised FLC levels suggest impaired immunoglobulin assembly [3]. Importantly, raised FLC levels in sepsis could also result from release of stored light chains during accelerated B-lymphocyte death [8] and impaired excretion due to renal dysfunction, independent of immunoglobulin assembly.

Intravenous immunoglobulins and previous clinical trials in adults with sepsis

Intravenous immunoglobulins are produced by pooling together of serum immunoglobulins from multiple donors. There are two types of intravenous immunoglobulin products – IVIG containing only IgG and IVIGAM containing IgG, IgA, and IgM. The newer IVIGAM products contain higher levels of IgM. The manufacturing processes, concentrations of different immunoglobulins and the herd immunity of the donors influence the therapeutic effects of IVIG/IVIGAM [1]. The pleiotropic immunomodulatory properties of IVIG are mediated through Fc gamma receptors (FcγR), scavenging of mediators, by negating the biological effects of B-lymphocyte apoptosis and replenishing low immunoglobulins in sepsis [1]. Infection and sepsis increase leukocyte FcγR expression. As the relative expression of inhibitory FcγRIIB versus stimulatory FcγR in sepsis patients is unknown, the extent of immunomodulation with IVIG/IVIGAM therapy may unpredictably differ between patients.

Systematic reviews of randomized controlled trials (RCTs) have showed potential benefits of IVIG/IGAM in sepsis, but important limitations preclude their utilization as a standard of care therapy in sepsis patients [9, 10]. Key limitations include variable trial quality, uncertainty around best responder characteristics, the ideal preparation IVIG vs IVIGAM, or the dosage regimen, timing, duration of therapy, low product availability and lack of cost effectiveness data (Table 1) [9, 10]. Importantly, although IVIG are often used in sepsis from group A streptococcus infection, the level of evidence that could support such recommendation is lower than for the overall population of patients with sepsis [9, 10]. In addition, IVIG/IVIGAM therapy is associated with adverse reactions such as fever, headache, thromboembolic events, renal dysfunction, aseptic meningoencephalitis, anaphylaxis, and detrimental effects of the positive fluid balance on outcomes such as respiratory dysfunction [9, 10]. These issues also highlight the need for better designed IVIG/IVIGAM trials.

Designing future intravenous immunoglobulins trials in sepsis

Sepsis is a heterogeneous illness. Sepsis characteristics such as site of infection and organ dysfunction influences mortality differently [11]. Sepsis related host responses differ by site of infection [12]. These differences may lead to different IVIG/IVGAM treatment effects in trials. These differences could also inform IVIG/IVIGAM treatment responder characteristics (predictive enrichment) or identify subpopulations (such as patients with exaggerated inflammation) who benefit the most in future trials [13]. As the biological rationale for IVIG/IVIGAM therapy is immunomodulation, the highest tolerated dose with the greatest potential effect need to be determined. Phase II clinical trials looking at identifying dominant mechanism affecting endogenous immunoglobulin pathways could also inform future trials. For example, patients with low levels of immunoglobulins with concurrently raised free light chains imply impaired immunoglobulin production which may be a major mechanism contributing to death in sepsis. Interventional cohort studies highlight the potential utility of immunoglobulin therapy in patients with multidrug resistant bacterial infections [14] and in patients with sepsis associated coagulopathy [15], which should be followed through to inform future immunoglobulin trials in sepsis.

Conclusions

Immunoglobulin and B-lymphocyte homeostasis is acutely altered in sepsis. Despite biological plausibility, further trials addressing the limitations in current evidence base are required prior to using intravenous immunoglobulins as adjuvant therapy for sepsis patients.

Conflict of interest declaration:

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Legends

Table-1: Reasons precluding the current use of IVIG/IVGAM in sepsis [9]

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Table-1: Reasons precluding the current use of IVIG/IVGAM in sepsis [9]

Parameter	Explanation from previous trials
Trial quality	Many of these trials were small, were prone to bias primarily due to lack of blinding, had suboptimal adverse event reporting and had low quality when evaluated using standard randomised controlled trial quality assessment instruments.
Population	The trial populations varied in specific characteristics such as infection site, illness severity and organ dysfunction. In meta-analysis of trials, patients with higher illness severity (severe sepsis and shock vs. sepsis) were more likely to benefit from IVIG/IVIGAM therapy.
Product	In meta-analysis of trials, IVIGAM had a higher treatment effect compared to IVIG, albeit with significant between trial heterogeneity. Thus, the ideal therapeutic product to use in sepsis patients is unknown. Further, the IVIG/IVIGAM products used differed between trials and this may have contributed to differences in the beneficial (and/or adverse) immunomodulatory effects.
Dosing, timing and duration of therapy	Trials have tested widely different IVIG/IVIGAM doses (between 0.2 to 2 g/kg) and different treatment durations (from 2 to 7 days). At low doses only replacement of low immunoglobulin levels is achieved. For immunomodulation, doses greater than 0.5g/kg are required. In meta-analysis of trials, patients receiving higher doses (≥1 g/kg vs. <1 g/kg) over a longer period (more than 2 days) may benefit more from IVIG/IVIGAM therapy.
Mechanism of action	Exact mechanism(s) by which intravenous immunoglobulins provide benefit to sepsis patients are unclear. Therefore, no trial to date had targeted or evaluated specific mechanisms, other than generic improvements in inflammation.
Adverse effects	Although IVIG/IVIGAM products have several adverse effects well observed in clinical studies. Some of the adverse effect overlap with sepsis manifestations and as such the safety of these products still remains uncertain.
Availability and costs	IVIG/IVGAM being a blood product coming from several human donors, its production is resource intensive, costly and limited in capacity. The cost effectiveness of IVIG/IVIGAM in sepsis remains uncertain.

Standard of care	Most trials were conducted more than a decade ago, when the standard of early sepsis management (resuscitation goals, fluids and antibiotic therapy) were different. Therefore, an argument often highlighted is that the IVIG/IVIGAM treatment effects were observed in the context of a suboptimal early sepsis care.